1 560 406

PATENT SPECIFICATION

(11) 1 560 406

(21) Application No. 42907/76 (22) Filed 15 Oct. 1976
(31) Convention Application No. 2546577
(32) Filed 17 Oct. 1975 in
(33) Federal Republic of Germany (DE)
(44) Complete Specification published 6 Feb. 1980
(51) INT CL³ A61K 31/48 31/74 47/00
(52) Index at acceptance
A5B 828 829 832 L

(72) Inventors LOTHAR EHRHARDT
VOLKER HARTMANN
LUDWIG PATT and
KARL-HEINZ OTTO

(54) SOLID SOLUTIONS OF ERGOT ALKALOIDS IN POLYMERS

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new pharmaceutical compositions of ergot alkaloids.

The invention provides pharmaceutical compositions comprising a solid solution of one or more ergot alkaloids in a pharmaceutically acceptable solid polymer which is soluble or swellable in gastric juices.

In the term "ergot alkaloids" is included naturally occurring ergot alkaloids for example ergotamine, ergocristine, ergocrypine and ergocornine; their synthetic derivatives, for example ergovaline; their hydrogenated forms, for example dihydroergotamine, and the salts of any of these. Suitable salts are those derived from pharmaceutically acceptable acids, for example organic acids such as methanesulphonic, tartaric and maleic acids or inorganic acids such as hydrochloric acid.

Preferably the polymer is a polyalkylene glycol, polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinyl acetate or a mixture of these. If mixtures of polymers are used, the proportion of different polymers in the mixture is not critical: preferably, however, equal quantities of two or three different polymers may be present In the case of mixtures, one or more of the polymers may be a liquid, for example a low molecular weight polyalkylene glycol, provided that the resulting mixture of polymers is a solid.

Suitable polyalkylene glycols include polyethylene glycol and polypropylene glycol and their copolymers having a molecular weight of 200 to 20,000, preferably 4000 to 15,000, more preferably 6000 to 13,000. By "polyvinylpyrrolidone" is meant uncrosslinked poly(N-vinyl)pyrrolidone, suitably of molecular weight between 10,000 and 100,000, preferably 11,500 to 40,000, more preferably 20,000 to 30,000. The copolymer of vinylpyrrolidone and vinyl acetate preferably contains 60% by weight vinylpyrrolidone and 40% by weight vinyl acetate and preferably has a molecular weight of 30,000 to 100,000, more preferaby 40,000 to 90,000.

The solid solution of ergot alkaloid in polymer may also contain certain additional pharmaceutically acceptable ingredients, particularly surfactants such as sodium lauryl sulphate or polyethylene glycol fatty acid esters, preferably polyethylene glycol stearate; and stabilisers such as acids, preferably methanesulphonic acid, maleic acid and tartaric acid, to adjust the pH of the composition. The preferred pH range for the composition is pH 4—6, preferably pH 4—5.

In the solid solution, the proportion by weight of ergot alkaloid to solid polymer together with surfacant and/or stabilizer, if present, may lie between 0.1:99.9 and 50:50, preferably between 5:95 and 15:85. Where surfactants and/or stabilisers are present, the proportion by weight of the surfactant and/or stabilizer to the ergot alkaloid is suitably from 1:45 to 10:1.

The solid solution of the invention is a true solid solution of the ergot alkaloid in the polymer; that is it consists of only one solid phase.

The invention also provides a process for the preparation of pharmaceutical compositions comprising the step of working up one or more ergot alkaloids into a solid solution in a pharmaceutically acceptable solid polymer which is soluble or swellable in gastric juices, preferably consisting of a

polyalkylene glycol, polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinyl acetate, or a mixture of these. The solid solution may be used without further admixture, or may be compounded in known manner with one or more conventional pharmaceutically acceptable excipients, and optionally with additional active ingredients.

Preferably, the solid solution is obtained by dissolving the ergot alkaloid, the polymer and optionally any surfactant and/or stabiliser in a common solvent and evaporating to dryness the clear solution so obtained. Suitable solvents include lower alcohols, having from 1 to 4 carbon atoms, for example ethanol and methanol. The solids are suitably dissolved by stirring with the solvent at a temperature of from 30 to 70°C, preferaby 40—60°C, and the solvent may be removed by evaporation under vacuum at the same temperature. In the preparation of the solution it is also possible to add only a part of the polymer and the surfactant and/or stabilizer, if any, and to add the remainder during the evaporation of the solvent. The resulting clear solution is left to solidify at room temperature (15—25°C) and the solid solution may then be ground to a fine powder and dried, suitably under vacuum at 30°C, to remove all traces of the solvent.

The solid solution may be used in the preparation of galenic forms such as tablets and capsules. For this purpose it may be compounded with conventional excipients for example binding agents, lubricants, fillers and disintegrants, as well as colouring agents, sweeteners and flavouring agents.

In the preparation of tablets, calcium carbonate, sodium carbonate, lactose, starch and talc may be used as fillers; starch and alginic acid as granulating and disintegrating agents; starch and gelatine as binding agents and magnesium stearate, stearic acid and talc as lubricants. Common pharmaceutical retarding agents such as waxes, fats, cellulose derivatives and other polymers may also be used. The tablets may be uncoated or coated in known manner.

In the preparation of soft gelatine capsules, the solid solution is compounded in known manner for example with a mixture of glycerol, sorbitol and water together with preservative and optionally colouring matter. For filling hard gelatin capsules, the solid solution may be used along or compounded in known manner with pharmaceutically acceptable diluents or carriers.

The pharmaceutical compositions according to the present invention have the advantageous property of giving increased absorption of the ergot alkaloids into the bloodstream of the recipient, thereby enhancing the known pharmacological properties of the ergot alkaloids.

The following Examples illustrate the invention:

EXAMPLE 1:

34.6 g Dihydroergotamine methane sulphonate, 195.4 g polyvinylpyrrolidone (av. mol. wt. 25,000) and 500 ml methanol are charged into a 4 l round-bottomed flask, which is then attached to a rotary evaporator. The flask is rotated at a bath temperature of 60°C, until the flask contents reach 60°C, by which time a clear solution is obtained.

The bath temperature is maintained at 60°C and the pressure is reduced to approx. 250 Torr. Methanol is removed by evaporation until the residue has a syrupy consistency. The residue is decanted into an evaporating basin and left to solidify for two hours at room termpature. The solid residue is dried in a vacuum oven at 30°C, 1 Torr for 12 hours, ground to a fine powder and dried again.

EXAMPLE 2:

34.6 g Dihydroergotamine methanesulphonate, 193.2 g polyvinylpyrrolidone (av. mol. wt. 25,000) 2.26 g polyethylene glycol (1800) stearate and 500 g methanol are charged into a 4 l round-bottomed flask. The procedure of Example 1 is repeated, to obtain a dry powdered mixture.

EXAMPLE 3:
Tablet Composition

The following ingredients are compounded together in conventional manner and formed into tablets in a tabletting press:

	parts by weight
Solid mixture of Example 1:	16.3
lactose	104.0
corn starch	15
talc	12
cellulose powder	32
silicon dioxide	0.7

EXAMPLE 4:
Composition for Soft Gelatin Capsules

The following ingredients are compounded together in conventional manner and the mixture used to fill soft gelatin capsules:

	parts by weight
Solid mixture of Example 1:	16.3
Glycerol	9
Polyethylene glycol 400	74.7

EXAMPLE 5:
Composition for Hard Gelatin Capsules

The following ingredients are compounded together in conventional manner and the mixture used to fill hard gelatin capsules:

	parts by weight
Solid mixture of Example 1:	16.3
Silicon dioxide	0.7
corn starch	13
lactose	65

EXAMPLES 6—8

Examples 3—5 are repeated using the solid mixture of Example 2.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a solid solution of one or more ergot alkaloids, as herein defined, in a pharmaceutically acceptable solid polymer which is soluble or swellable in gastric juices, optionally together with a pharmaceutically acceptable surfactant and/or stabiliser, the proportion by weight of ergot alkaloid to solid polymer together with surfactant and/or stabiliser, if present, being from 0.1:99.9 to 50:50, said composition being capable of giving increased absorption of ergot alkaloid into the bloodstream of the recipient.

2. A composition as claimed in Claim 1 in which the polymer is a polyalkylene glycol, uncrosslinked poly(n-vinyl)pyrrolidone, a copolymer of vinylpyrrolidone and vinyl acetate, or a mixture of these.

3. A composition as claimed in Claim 2 in which the polymer is polyethylene glycol, polymethylene glycol or a copolymer of these, having a molecular weight of 200 to 20,000.

4. A composition as claimed in Claim 3 in which the polymer has a molecular weight of from 4000 to 15,000.

5. A composition as claimed in Claim 4 in which the polymer has a molecular weight of from 6000 to 13,000.

6. A composition as claimed in Claim 2 in which the polymer is uncrosslinked poly(N-vinyl)pyrrolidone of molecular weight from 11,500 to 40,000.

7. A composition as claimed in Claim 6 in which the polymer has a molecular weight of from 20,000 to 30,000.

8. A composition as claimed in Claim 2 in which the polymer is a copolymer of vinylpyrrolidone and vinyl acetate, having a molecular weight of from 30,000 to 100,000.

9. A composition as claimed in Claim 8 in which the polymer has a molecular weight of from 40,000 to 90,000.

10. A composition as claimed in any one of Claims 2, 8 or 9, in which the polymer is a copolymer of 60% by weight vinylpyrrolidone and 40% by weight vinyl acetate.

11. A composition as claimed in any one of the preceding claims in which the solid solution contains a pharmaceutically acceptable surfactant and/or stabiliser in addition to the ergot alkaloid and the solid polymer.

12. A composition as claimed in Claim 11 in which the proportion by weight of the surfactant and/or stabiliser to the ergot alkaloid is from 1:45 to 10:1.

13. A composition as claimed in any one of the preceding claims in which, in the solid solution, the proportion by weight of ergot alkalid to solid polymer together with surfactant and/or stabiliser, if present, is from 5:95 to 15:85.

14. A composition as claimed in any one of the preceding claims comprising the solid solution in association with one or more conventional pharmaceutically acceptable excipients.

15. A composition as claimed in any one of the preceding claims, in the form of a tablet.

16. A composition as claimed in any one of Claims 1—14, in the form of a capsule.

17. A pharmaceutical composition substantially as described in any one of the Examples.

18. A process for the production of a pharmaceutical composition comprising the step of dissolving one or more ergot alkaloids and a pharmaceutically acceptable solid polymer selected from polyalkylene glycols, uncrosslinked poly-(N-vinyl)pyrrolidone, copolymers of vinylpyrrolidone and vinyl acetate, or mixtures of these in a common solvent which is then removed by evaporation to give a solid solution of the ergot alkaloid in the polymer.

19. A process as claimed in Claim 18 in which the solvent is a lower alcohol having from 1—4 carbon atoms.

20. A process as claimed in Claim 19 in which the solvent is methanol.

21. A process as claimed in any one of Claims 18—20 in which the solution and evaporation steps are carried out at a temperature between 40 and 60°C.

22. A process as claimed in any one of Claims 18—21 in which the residue from evaporation of the solvent is solidified, ground to a powder and dried.

23. A process as claimed in any one of Claims 18—22 in which the solid solution is compounded in known manner with one or

more pharmaceutically acceptable excipients and formed into tablets or capsules.

24. A pharmaceutical composition whenever produced by the process of any one of Claims 18—23.

B. A. YORKE & CO.,
Chartered Patent Agents,
98 The Centre,
Feltham,
Middlesex TW13 4EP,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.